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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,794	10/05/2001	Jennifer L. Hillman	PF-0565 USN	4717
	7590 10/09/2003		EXAMINER	
Incyte Genomics Inc Legal Department 3160 Poter Drive Palo Alto, CA 94304			STEADMAN, DAVID J	
			ART UNIT	PAPER NUMBER
			1652	

DATE MAILED: 10/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/744,794	Applicant(s) HILLMAN ET AL.	
	Examiner David J Steadman	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 July 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 21-45 is/are pending in the application.
- 4a) Of the above claim(s) 21-23,31 and 34-44 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 24-30,32,33 and 45 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>7/30/03</u> . | 6) <input type="checkbox"/> Other: _____. |

DETAILED ACTION

Status of the Application

[1] Claims 21-45 are pending in the application.

[2] Applicant's amendment to the specification, cancellation of claims 1-20, and addition of claims 21-45 in an amendment filed July 16, 2003, is acknowledged.

[3] It is noted that in the sequence listing filed April 22, 2002, SEQ ID NO:38 is listed as the corresponding encoding nucleic acid for the polypeptide of SEQ ID NO:7. However, in the latest sequence listing filed November 21, 2002, SEQ ID NO:37 is listed as the corresponding encoding nucleic acid for the polypeptide of SEQ ID NO:7. The nucleic acid sequences and corresponding encoded polypeptide sequences in the restriction mailed June 12, 2003 were grouped together based on the earlier sequence listing filed April 22, 2002 and consequently SEQ ID NO:38 is listed in the restriction mailed June 12, 2002 as the corresponding encoding nucleic acid for the polypeptide of SEQ ID NO:7. In a telephone conversation with Mr. Richard C. Ekstrom on September 25, 2003, this was brought to applicant's attention. Applicant notified the examiner that the election of claims drawn to a nucleic acid encoding the polypeptide of SEQ ID NO:7 was correct. However, applicant noted that in view of the change in numbering of the sequence identifiers, the elected nucleic acid sequence should have been SEQ ID NO:37 instead of SEQ ID NO:38. In the interest of advancing prosecution, the claims have been examined as though they recite SEQ ID NO:37 instead of SEQ ID NO:38.

[4] Applicant's election with traverse of Group XXXVIII, original claims 3-13, drawn to a polynucleotide encoding SEQ ID NO:7 including SEQ ID NO:37 is acknowledged.

Lack of Unity

[5] Applicant traverses the lack of unity requirement (beginning at page 8 of the July 16, 2003 amendment) by stating that the unity of invention standard must be applied in national stage applications. Applicant cites sections of MPEP § 1800 in support of their statements. In response to applicant's statements, it is noted that the unity of invention standard was applied to original claims 1-20 in evaluating the claims for unity of invention and restriction practice according to 35 U.S.C. 121 and 372. MPEP § 1893.03(d) states, "If the examiner finds that a national stage application lacks unity of invention under § 1.475, the examiner may in an Office action require the applicant in the response to that action to elect the invention to which the claims shall be restricted". Also, according to PCT Rule 13.2, unity of invention exists only when the shared same or corresponding technical feature is a contribution over the prior art. As stated in the Office action mailed June 12, 2003, the inventions of original claims 1-20 do not relate to a single general inventive concept because the shared technical features of the claimed polypeptide and polynucleotide lack novelty or inventive step and therefore, do not make these technical features a contribution over the prior art. See the Office action mailed June 12, 2003 for those reasons why the inventions of original claims 1-20 lack unity of invention. In accordance with MPEP § 1893.03(d), the examiner properly applied the unity of invention standard to original claims 1-20 in the instant application.

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Beginning at the bottom of page 8 of the amendment filed July 16, 2003, applicant cites Example 17, Part 2 of Annex B to the Administrative Instructions Under the PCT, which states:

Example 17

Claim 1: Protein X.

Claim 2: DNA sequence encoding protein X.

Expression of the DNA sequence in a host results in the production of a protein which is determined by the DNA sequence. The protein and the DNA sequence exhibit corresponding special technical features. Unity between claims 1 and 2 is accepted.

Applicant argues the examiner should withdraw the lack of unity requirement with respect to claims 21-30 and 32-45. Applicant argues unity of invention exists for claims drawn to the polypeptide of SEQ ID NO:7 and claims drawn to the elected corresponding encoding polynucleotide of SEQ ID NO:37 based on the rules concerning unity of invention under the PCT and Example 17 as stated above. Applicant's argument is not found persuasive. According to PCT Rule 13.2, unity of invention exists only when there is a shared same or corresponding special technical feature among the claimed inventions. The polynucleotide of claim 33, which is drawn to an isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 32, encompasses polynucleotides that, when expressed, result in the production of proteins that do *not* correspond to the polypeptide of claims 21-23. Therefore, the polynucleotide of Group XXXVIII, particularly the polynucleotide of claim 33, does not share a corresponding special technical feature with the polypeptide of claims 21-23, and thus the inventions do not have unity of invention. Furthermore, according to PCT Rule 13.2, unity of invention exists only when the shared same or corresponding technical feature is a contribution over the prior art. The polypeptide of claims 21-23 and

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the polynucleotide of elected Group XXXVIII do not have unity of invention because the technical feature of the polypeptide of claims 21-23 and the polynucleotide of Group XXXVIII do not contribute over the prior art. The technical feature of claims 21-23 is a polypeptide, which is shown by Sigma Chemical Company 1993 Catalog (page 1067) to lack novelty or inventive step because Sigma Chemical Company 1993 Catalog teaches a Tyr-Arg bioactive peptide, corresponding to amino acids 286 and 287 of SEQ ID NO:7, and does not make it a contribution over the prior art. Also, the technical feature of Group XXXVIII is a polynucleotide, which is shown by Database GenBank Accession Number M61906 (gi:189424) (cited as reference 18 in the IDS filed July 30, 2003) to lack novelty or inventive step because Database GenBank Accession Number M61906 teaches a polynucleotide comprising at least 60 contiguous nucleotides of SEQ ID NO:37 (see attached sequence alignment) and does not make it a contribution over the prior art.

Beginning at the middle of page 9 of the amendment filed July 16, 2003, applicant argues unity of invention exists among all of the pending claims. Applicant argues the claimed polypeptides and encoding polynucleotides are corresponding technical features, which are common to all pending claims, which serve to technically interrelate all pending claims, and which define the contribution over the prior art. Applicant argues the pending claims are linked to form a single general inventive concept, and applicant is therefore entitled to prosecute all pending claims in a single application. Applicant's argument is not found persuasive. As stated above, the polynucleotide of Group XXXVIII does not share a corresponding special technical

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feature with the polypeptide of claims 21-23 and 37 and neither of the shared technical features of the polynucleotide of Group XXXVIII and the polypeptide of claims 21-23 makes a contribution over the prior art. As stated above, the polynucleotide of Group XXXVIII and the polypeptide of claims 21-23 and 37 do not constitute a special technical feature and thus there is no inventive link between the claimed polynucleotide, polypeptide, and the antibody of claim 31. Furthermore, 37 CFR § 1.475(d) does not provide for the inclusion of multiple methods of use within the main invention. As claim 30 is the first claimed method of using the polynucleotide of Group XXXVIII, this claim will be included and co-examined with the claims of Group XXXVIII. However, the *additional* methods of use of the polynucleotide of Group XXXVIII and methods of using the polypeptide of claims 21-23 and 37 do not have unity of invention in accordance with PCT Rule 13.2 and 37 CFR § 1.475(d). Therefore, the polynucleotide of Group XXXVIII, the polypeptide of claims 21-23 and 37, the antibody of claim 31, *additional* methods of using the polynucleotide of Group XXXVIII, and methods of using the polypeptide of claims 21-23 and 37 do not have unity of invention. It is noted that in the original claim groupings of the Office action mailed June 12, 2003, the examiner included claim 7, drawn to a method for detecting a polynucleotide, as the first claimed method of using the polynucleotide of Group XXXVIII. However, due to applicant's re-ordering of claims in the amendment filed July 16, 2003, claim 30, drawn to a method of producing a polypeptide using a cell comprising a recombinant polynucleotide, is now the first claimed method of using the polynucleotide of Group XXXVIII and will be co-examined in accordance with 37 CFR § 1.475(d).

Beginning at the top of page 10 of the amendment filed July 16, 2003, applicant argues there is minimal additional burden to examine the claims of Group VII (polypeptide and method of use claims) and LXIX (antibody claims). Applicant's argument is not found persuasive. 4.

While publications disclosing polynucleotide sequences with defined open reading frames *may* disclose the corresponding polypeptide sequences, it is false to assume the only source of a polypeptide is one in which the polynucleotide sequence is disclosed. Polypeptides can be purified from natural sources in the absence of polynucleotide information. Therefore, in order to search the claims of Groups XXXVIII AND VII, the examiner must search not only for polynucleotide sequences, but also for corresponding polypeptide sequences as well as for isolated polypeptides which are inherently identical to the claimed polypeptide with a defined sequence. The search for inherently identical polypeptides is a text-based search, independent of a polypeptide sequence search, and resulting publications must be assessed for their inherent applicability to the polypeptide claimed. Thus, a serious search burden would be required for the examiner to search not only the polynucleotide sequences, but also the polypeptide sequences as well as inherently identical polypeptides which is required by the claim language. The above reasoning also holds true for the search burden on the examiner to additionally search the antibody to the polypeptide whose polynucleotide sequence has been elected. Additionally, an appropriate search for antibodies which bind a polypeptide not only includes an extensive search of the polypeptide sequence, but also includes an extensive search of antibodies which bind similar polypeptides to

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assess their ability to bind the claimed polypeptide and thus act as an antibody to the claimed polypeptide. Thus, a serious search burden would be required for the examiner to search not only the polynucleotide sequences, but also the antibodies which bind the encoded polypeptides. While the search for polynucleotides will overlap with portions of the searches for encoded polypeptides and antibodies to said polypeptides, clearly the searches for polypeptides and antibodies are much more extensive resulting in a search burden on the Examiner to search all three distinct inventions.

While not addressed by applicant, it is noted that the polynucleotide of Group XXXVIII and the microarray of claim 45 share the same special technical feature, i.e., the polynucleotide of Group XXXVIII. Therefore, claim 45 will be co-examined with the claims of Group XXXVIII.

[6] The requirement is still deemed proper and is therefore made FINAL.

[7] Claims 21-23, 31, and 34-44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

[8] Claims drawn to an isolated polynucleotide, a recombinant polynucleotide, a cell, and a microarray (claims 24-29, 32-33, and 45) and the first claimed method of use, i.e., a method of producing a polypeptide using a cell transformed with a recombinant polynucleotide (claim 30), are being examined on the merits.

Specification/Informalities

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[9] It is noted that the specification has been amended (amendment filed July 16, 2003) so as to claim priority under 35 USC 119(e) to provisional applications as follows:

This application is a national stage application under 35 U.S.C. §371 of international patent application PCT/US99/17132, filed July 28, 1999, which claims the benefit of provisional application U.S. Ser. No. 60/155,213, filed July 28, 1998; provisional application U.S. Ser. No. 60/155,196, filed September 14, 1998; provisional application U.S. Ser. No. 60/155,239, filed October 14, 1998; provisional application U.S. Ser. No. 60/106,889, filed November 3, 1998; provisional application U.S. Ser. No. 60/109,093, filed November 19, 1998; provisional application U.S. Ser. No. 60/113,796, filed December 22, 1998; and provisional application U.S. Ser. No. 60/155,233, filed January 12, 1999.

The specification is objected to because the filing dates of the disclosed provisional applications do not correspond to filing dates provided in the declaration shown below:

<u>Application Serial No.</u>	<u>Filed</u>	<u>Status (Pending, Abandoned, Patented)</u>
60/155,213	June 9, 1999	Expired
60/155,196	July 14, 1999	Expired
60/155,239	July 15, 1999	Expired
60/106,889	Nov. 3, 1998	Expired
60/109,093	Nov. 19, 1998	Expired
60/113,796	Dec. 22, 1998	Expired

The filing dates of the provisional applications as disclosed in the amendment to the specification appears correct, while the filing dates stated in the declaration do not appear to be correct. It is suggested that applicant make the appropriate correction.

Claim Objections

[10] Claims 24-30, 32, 33, and 45 are objected to as reciting non-elected subject matter, i.e., SEQ ID NO:38, or being dependent upon non-elected claims. It is suggested that, for example, applicant amend the claims such that they recite SEQ ID

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NO:37 instead of SEQ ID NO:38 and/or no longer depend from non-elected claims 21-23.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

[11] Claims 24-30, 32-33, and 45 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or well-established utility. Claims 24-28, 32, and 33 are drawn to an isolated polynucleotide encoding SEQ ID NO:7 including SEQ ID NO:37 and variants and fragments thereof. Claim 29 is drawn to a cell transformed with the recombinant polynucleotide of claim 28. Claim 30 is drawn to a method of producing a polypeptide of SEQ ID NO:7 and variants and fragments thereof. Claim 45 is drawn to a microarray comprising the polynucleotide of claim 33.

The claimed polynucleotide has no substantial utility as further experimentation is required to establish its "real world" use as explained in detail below. It is noted that applicant asserts the polypeptide of SEQ ID NO:7 (encoded by SEQ ID NO:37) functions as a phosphorylation effector (page 3, lines 21-29 of the specification). The specification further provides the following information regarding the function of SEQ ID NO:7 (page 54 of the instant specification):

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Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
7	454	S57 S69 S130 T203 T212 S338 S420 S91 T101 T220 S271 S295 T315 S359 S381 Y197	N55 N140 N218 N403 N437 N441	SH2 domain: W63-Y138, W354-Y428 PI 3 kinase P85 regulator: K153-G176, A216- N257, R287-N332	phosphatidyl- inositol 3- kinase	PFAM BLOCKS PRINTS BLAST

As the specification fails to disclose the definition of the term “phosphorylation effector”, the examiner is left to make his own interpretation of the function of a “phosphorylation effector”. The term “effector” is defined as “[a] small molecule that when bound to an allosteric site of an enzyme causes either a decrease or an increase in the activity of the enzyme” according to “The American Heritage Dictionary of the English Language, Fourth Edition”, 2000, Houghton Mifflin Company, Boston MA. In view of this definition and the information provided at page 54 of the specification, one of ordinary skill in the art may conclude that the function of the polypeptide encoded by SEQ ID NO:37 is a PI-3 kinase effector. However, it is noted that the specification discloses that the activity of the polypeptide encoded by SEQ ID NO:37 can be measured by a kinase assay OR a phosphatase assay and the specification provides no indication as to which of the activity assays should be used to measure the activity of the polypeptide encoded by SEQ ID NO:37. Furthermore, in a provisional application to which applicant claims priority (provisional application 60/106,889) under 35 USC 119(e), the polypeptide encoded by SEQ ID NO:37 has been assigned the function of a kinase. (In the interest of clarity, it is noted that SEQ ID NO:3 as disclosed in provisional application 60/106,889 is the same as SEQ ID NO:7 of the instant application.) Page 12, lines 24-26 of provisional application 60/106,889 discloses, “[t]he invention features... .kinase

family members” (page 3, line 5 of the specification) and that the polypeptide of SEQ ID NO:3 of 60/106,889 has “potential phosphatidylinositol 3-kinase domains” (page 12, lines 24-26 of the specification) and that the kinase activity of the polypeptide of SEQ ID NO:3 60/106,889 can be measured by kinase assay (page 41, lines 20-28 of the specification). In view of this disclosure a skilled artisan may conclude that the polypeptide encoded by SEQ ID NO:37 exhibited PI-3 kinase activity. However, based on the results of a sequence search, it appears the polypeptide encoded by SEQ ID NO:37 is related at the amino acid level to a 55 kDa regulatory subunit of PI-3 kinase as disclosed by Inukai et al. (*J Biol Chem* 271:5317-5320). It is known in the art that the regulatory subunit of PI-3 kinase has no catalytic activity (see, e.g., Klippel et al. in *Mol Cell Biol* 13 :5560-5566). Therefore, in view of the contradictory teachings of the instant application (which appears to teach the polypeptide encoded by SEQ ID NO:37 is a PI-3 kinase effector whose activity can be measured by both a kinase and phosphatase assay), provisional application 60/106,889 (which teaches the polypeptide encoded by SEQ ID NO:37 has kinase activity that can be measured by kinase assay) and the prior art (which teaches a highly homologous encoding nucleic acid encodes a protein without kinase activity), it is unclear as to the biological function or significance of the polypeptide encoded by SEQ ID NO:37.

Therefore, one of ordinary skill in the art would recognize that, in view of the confusing and contradictory teachings of the instant specification, provisional application 60/106,889, and the prior art, further experimentation is required to establish a “real world” use for the polynucleotide of SEQ ID NO:37. This type of utility is not considered

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a "substantial utility". See e.g., *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966). The specification must teach a skilled artisan how to use what is claimed and not merely provide a blueprint for further experimentation in order for an artisan to identify a use for the claimed invention. As stated in *Brenner v. Manson*, 383 U.S. 519 535-536, 148 USPQ 689, 696 (1966), "[a] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion". Here the specification fails to provide a specific benefit in currently available form for the claimed polynucleotide as the claimed polynucleotide is suitable only for additional research in order that one of ordinary skill in the art may determine the biological function and/or significance of the claimed polynucleotides.

Applicant asserts various utilities for the claimed polynucleotide including use "for the diagnosis, treatment, or prevention of cell proliferative, immune, and neuronal disorders" (see e.g., page 13, lines 20-21 and pages 24-37 of the specification). However, the specification fails to disclose any specific cell proliferative, immune, and neuronal disorders that can be diagnosed, treated, or prevented using the claimed polynucleotides. In the absence of such disclosure, one of ordinary skill in the art is left to determine which – if any - cell proliferative, immune, and neuronal disorders can be diagnosed, treated, or prevented using the claimed polynucleotide and the specific conditions necessary for such. The specification further discloses the use of the claimed polynucleotides for protein expression and hybridization. However, these utilities are not specific as *any* polynucleotides have such use. Therefore, the asserted utilities are not

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specific to the claimed polynucleotide and are instead general utilities that would be applicable to the broad class of polynucleotides.

For the reasons stated above, the claimed polynucleotide has no specific and substantial utility.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[12] Claims 24, 28-30, and 32-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claim 24 (claims 28-30 dependent therefrom) is indefinite in the recitation of "biologically active". The specification discloses the meaning of this term as "having structural, regulatory, or biochemical functions of a naturally occurring molecule" (page 8, lines 4-5 of the specification). However, the scope of biological activities encompassed by this term is vague and it is unclear from this definition as to what functions of the encoded polypeptide of SEQ ID NO:7 applicant intends as the meaning of "biologically active". It is suggested that the term "biologically active" be replaced with a term that clearly defines applicant's intended biological function.

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[b] Claim 27 is unclear because SEQ ID NO:38 does not encode the polypeptide of SEQ ID NO:7 as explained in detail in item 4 above. It is suggested that applicant replace "SEQ ID NO:38" with "SEQ ID NO:37".

[c] Claim 32 (claim 33 dependent therefrom) is indefinite in the recitation of "complementary". The specification defines the term "complementary" as, "'partial' such that only some of the nucleotides bind" or "'complete' such that total complementarity exists between the single stranded molecules" (page 8, lines 12-13 of the specification). As such, it is unclear as to whether the complementary polynucleotides are partial or complete complements. In the interest of advancing prosecution, the term "complementary" has been interpreted as completely complementary. If the examiner's interpretation of the term is incorrect, applicant should so state and clarify the record. It is suggested that applicant clarify the meaning of the term "complementary" as being either a partial or complete complement.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[13] Claims 24, 26, 28-30, 32-33, and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s)

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contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 24 (claims 28-30 and 45 dependent therefrom) and 26 are drawn to a genus of isolated polynucleotides encoding a polypeptide comprising a naturally occurring amino acid sequence that is at least 90% identical to SEQ ID NO:7 (claims 24 and 26) and biologically active and immunogenic fragments of a polypeptide having SEQ ID NO:7 (claim 24). Claim 30 is drawn to a method for producing a genus of polypeptides using a cell comprising a genus of recombinant polynucleotides encoding a polypeptide comprising a naturally occurring amino acid sequence that is at least 90% identical to SEQ ID NO:7 and biologically active and immunogenic fragments of a polypeptide having SEQ ID NO:7. Claim 32 is drawn to an isolated polynucleotide comprising a naturally occurring sequence at least 90% identical to SEQ ID NO:37, a complement thereof, and RNA equivalents thereof. Claim 33 is drawn to an isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 32. It is noted that only those parts of claims 24, 30, and 32 relevant to the instant rejection have been stated above.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a *representative number of species* by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or

disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species of the genus of claimed polynucleotides, i.e., the polynucleotide of SEQ ID NO:37. The specification fails to describe any additional representative species of the claimed genus. While MPEP § 2163 acknowledges that in certain situations “one species adequately supports a genus”, it is also acknowledges that “[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus”. In the instant case, the claimed genus of polynucleotides encompasses species that are widely variant in both structure and function, including (but not limited to) genomic sequences, allelic variants, and nucleic acid variants encoding polypeptides having function other than the activity of SEQ ID NO:7, e.g., non-functional polypeptides and polypeptides having activity other than the asserted kinase effector activity. As such, the disclosure of the single representative species of SEQ ID NO:37 is insufficient to be representative of the attributes and features of *all* species encompassed by the claimed genus of polynucleotides. Given the lack of description of a representative number of polynucleotides, the specification fails to sufficiently

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describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[14] Claims 24-30, 32-33, and 45 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial or specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

[15] Even if applicant demonstrates the polynucleotide encoding SEQ ID NO:7 has a specific and substantial or well-established utility, the following rejection still applies. Claims 24, 26, 28-30, 32-33, and 45 are rejected under 35 U.S.C. 112, first paragraph, because the specification is not enabling for the broad scope of claimed polynucleotides and polypeptides produced using said polynucleotide. Regarding claims 24 (claims 28, 29, and 45 dependent therefrom), 26, 32, and 33, the specification, while being enabling for a polynucleotide encoding SEQ ID NO:7 including SEQ ID NO:37, does not reasonably provide enablement for the broad scope of claimed polynucleotides, including *all* polynucleotides encoding polypeptides comprising a naturally occurring amino acid sequence that is at least 90% identical to SEQ ID NO:7, *all* polynucleotides encoding biologically active and immunogenic fragments of a polypeptide having SEQ ID NO:7, *all* polynucleotides comprising a naturally occurring sequence at least 90% identical to SEQ ID NO:37 and complements and RNA equivalents thereof, and *all* polynucleotides comprising at least 60 contiguous nucleotides of the polynucleotide of

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claim 32. Regarding claim 30, the specification, while being enabling for a method of producing the polypeptide of SEQ ID NO:7 using a cell transformed with a polynucleotide encoding SEQ ID NO:7, does not reasonably provide enablement for a method for producing the broad scope of polypeptides of claim 21. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: The claims are so broad as to encompass *all* polynucleotides encoding polypeptides comprising a naturally occurring amino acid sequence that is at least 90% identical to SEQ ID NO:7, *all* polynucleotides encoding biologically active and immunogenic fragments of a polypeptide having SEQ ID NO:7,

all polynucleotides comprising a naturally occurring sequence at least 90% identical to SEQ ID NO:37 and complements and RNA equivalents thereof, *all* polynucleotides comprising at least 60 contiguous nucleotides of the polynucleotide of claim 32, and a method for producing *all* polypeptides of claim 21 using *all* recombinant polynucleotides encoding therefor. The broad scope of claimed polynucleotides or polynucleotides recited in the method of claim 30 are not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides broadly encompassed by the claims. In this case the disclosure is limited to a polynucleotide encoding SEQ ID NO:7 including SEQ ID NO:37 and a method of producing the polypeptide of SEQ ID NO:7 using a host cell transformed with a polynucleotide encoding SEQ ID NO:7.

- The lack of guidance and working examples: The specification provides only a single working example of the claimed polynucleotide, i.e., SEQ ID NO:37 and only a single working example of a polypeptide produced using a host cell transformed with a recombinant polynucleotide, i.e., SEQ ID NO:7. These working examples fail to provide the necessary guidance for making and/or using the entire scope of polynucleotides. The specification fails to provide guidance regarding those nucleotides of SEQ ID NO:37 or amino acids of SEQ ID NO:7 that may be altered by substitution, addition, insertion, and/or deletion with an expectation of maintaining the desired activity. Furthermore, the specification fails to provide guidance as to how to use those variant nucleic acids – both naturally and non-naturally occurring - that encode polypeptides

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having activities other than the desired activity, e.g., nucleic acids encoding non-functional polypeptides or polypeptides having activity other than SEQ ID NO:7.

- The high degree of unpredictability in the art: The nucleotide sequence of an encoding nucleic acid determines the corresponding encoded protein's structural and functional properties. Predictability of which changes can be tolerated in an encoded protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within an encoding nucleic acid's sequence where modifications can be made with a reasonable expectation of success in obtaining an encoded polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. In this case, the necessary guidance has not been provided in the specification as explained in detail above. Thus, a skilled artisan would recognize the high degree of unpredictability that the entire scope of polynucleotides would encode a polypeptide having the desired activity. The ability to assign a protein's function based on similarities to other proteins, even those that are naturally occurring, is *highly* unpredictable.
- The state of the prior art supports the high degree of unpredictability: The state of the art provides evidence for the high degree of unpredictability in altering a

polynucleotide sequence with an expectation that the encoded polypeptide will maintain the desired activity/utility. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). While it is acknowledged that this reference was published in 1991, to date there remains no certain method for reasonably predicting the effects of even a *single* amino acid mutation on a protein. Such mutations may even completely alter a protein's activity. As a representative example, Witkowski et al. (*Biochemistry* 38:11643-11650) teaches that a single amino acid substitution results in conversion of the parent polypeptide's activity from a beta-ketoacyl synthase to a malonyl decarboxylase (see e.g., Table 1, page 11647). Thus, the prior art acknowledges the unpredictability of altering a protein-encoding sequence with an expectation of obtaining a protein having a desired function and discloses that even a single substitution in a polypeptide's amino acid sequence may completely alter the function of a polypeptide.

- The amount of experimentation required is undue: While methods of generating variants of a given polynucleotide, e.g., mutagenesis, and methods of isolating homologous polynucleotides, e.g., hybridization, are known, it is not routine in the art to screen for *all* polynucleotides having a substantial number of substitutions or

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modifications and encoding polypeptides having *any* function, as encompassed by the instant claims. Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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[16] Applicant's claim for domestic priority under 35 USC § 119(e) to provisional applications 60/155,213, filed June 9, 1999; 60/155,196, filed July 14, 1999; 60/155,239, filed July 15, 1999; 60/106,889, filed November 3, 1998; 60/109,093, filed November 19, 1998; and 60/113,796 filed December 22, 1998 is acknowledged. The sequences of SEQ ID NO:7 and 37 of the instant application are disclosed in provisional application number 60/106,889 as SEQ ID NO:3 and 9, respectively. Applicant is granted the benefit of the earlier filing date of provisional application 60/106,889 to the extent this provisional application provides support for the claimed subject matter. Accordingly, the following rejection(s) have been made based on a priority date of November 03, 1998.

[17] Claims 24 and 33 are rejected under 35 U.S.C. 102(a) as being anticipated by Skolnik et al. (*Cell* 65:83-90). Claim 24 (in relevant part) is drawn to an isolated polynucleotide encoding a biologically active fragment of SEQ ID NO:7 and an immunogenic fragment of SEQ ID NO:7. Claim 33 is drawn to an isolated polynucleotide comprising at least 60 nucleotides of a polynucleotide of claim 32. Skolnik et al. teach a nucleic acid that is 100% identical to nucleotides 402-1698 of SEQ ID NO:37, encoding a biologically active and immunogenic fragment of SEQ ID NO:7 (page 85, Figure 3). This anticipates claims 24 and 33 as written.

[18] Claims 24 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Inukai et al. (*J Biol Chem* 271:5317-5320; cited as reference 14 in the IDS filed July 30, 2003) as evidenced by Database GenBank Accession Number D64048 (gi:1246393). Claim 24 (in relevant part) is drawn to an isolated polynucleotide encoding a polypeptide

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comprising a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO:7, a biologically active fragment of SEQ ID NO:7, and an immunogenic fragment of SEQ ID NO:7. Claim 26 is drawn to an isolated polynucleotide encoding a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO:7. Inukai et al. teach a nucleic acid encoding a polypeptide that is 98% identical to SEQ ID NO:7. Inukai et al. teach their nucleic acid has GenBank Accession Number D64048 (page 5317, left column, bottom). Database GenBank Accession Number D64048 discloses the nucleic acid sequence of Inukai et al. This anticipates claims 24 and 26 as written.

[19] Claim 33 is rejected under 35 U.S.C. 102(b) as being anticipated by Database GenBank Accession Number M61906 (gi:189424) (cited as reference 18 in the IDS filed July 30, 2003). Claim 33 is drawn to an isolated polynucleotide comprising at least 60 nucleotides of a polynucleotide of claim 32. GenBank Accession Number M61906 discloses the sequence of a nucleic acid that is at least 60 nucleotides of a polynucleotide of claim 32. This anticipates claim 33 as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

[20] Claims 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Inukai et al. as evidenced by Database GenBank Accession Number D64048. Claim 28 is drawn to a recombinant polynucleotide comprising a promoter operably linked to a polynucleotide of claim 24. Claim 29 is drawn to a cell transformed with the recombinant polynucleotide of claim 28. Claim 30 is drawn to a method for making a polypeptide encoded by a polynucleotide of claim 24.

Inukai et al. and Database GenBank Accession Number D64048 disclose the teachings as described above. Inukai et al. further teach “[o]ur future studies will focus on the variety of possible functions mediated by differences in the NH₂-terminal portions of the regulatory subunits of PI 3-kinase” (page 5320, right column, top). Inukai et al. do not teach their nucleic acid operably linked to a promoter, a host cell transformed therewith, or a method of making a polypeptide using said host cell.

Also, at the time of the invention, methods of removing a nucleic acid from a cloning vector and inserting said nucleic acid into an expression vector, transforming a host cell with said expression vector, and using said host cell to produce a polypeptide were well known in the art.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to insert the nucleic acid of Inukai et al. into an expression vector, transform a host cell with said expression vector, and use said host cell to produce a polypeptide. One would have been motivated to produce a polypeptide using a host cell transformed with an expression vector comprising the nucleic acid of Inukai et al. in order to study the function of the amino terminal portion of the polypeptide encoded by the nucleic acid

of Inukai et al. as described above. One would have a reasonable expectation of success for inserting the nucleic acid of Inukai et al. into an expression vector, transforming a host cell with said expression vector, and using said host cell to produce a polypeptide because of the results of Inukai et al. and the state of the art at the time of the invention. Therefore, claims 28-30, drawn to a recombinant polynucleotide, a cell, and a method of making a polypeptide as described above would have been obvious to one of ordinary skill in the art.

[21] Claims 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Skolnik et al. Claim 28 is drawn to a recombinant polynucleotide comprising a promoter operably linked to a polynucleotide of claim 24. Claim 29 is drawn to a cell transformed with the recombinant polynucleotide of claim 28. Claim 30 is drawn to a method for making a polypeptide encoded by a polynucleotide of claim 24. Claim 45 is drawn to a microarray comprising a polynucleotide of claim 33.

Skolnik et al. disclose the teachings as described above. Skolnik et al. further teach the role of the protein encoded by their nucleic acid is yet to be defined (page 88, right column, middle). Skolnik et al. do not teach their nucleic acid operably linked to a promoter, a host cell transformed therewith, or a method of making a polypeptide using said host cell.

Also, at the time of the invention, methods of removing a nucleic acid from a cloning vector and inserting said nucleic acid into an expression vector, transforming a host cell with said expression vector, and using said host cell to produce a polypeptide were well known in the art.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to insert the nucleic acid of Skolnik et al. into an expression vector, transform a host cell with said expression vector, and use said host cell to produce a polypeptide. One would have been motivated to produce a polypeptide using a host cell transformed with an expression vector comprising the nucleic acid of Skolnik et al. in order to study the function of the protein encoded by the nucleic acid of Skolnik et al. as suggested above. One would have a reasonable expectation of success for inserting the nucleic acid of Skolnik et al. into an expression vector, transforming a host cell with said expression vector, and using said host cell to produce a polypeptide because of the results of Skolnik et al. and the state of the art at the time of the invention. Therefore, claims 28-30, drawn to a recombinant polynucleotide, a cell, and a method of making a polypeptide as described above would have been obvious to one of ordinary skill in the art.

Conclusion

[22] Status of the claims:

- Claims 21-45 are pending.
- Claims 21-23, 31, and 34-44 are withdrawn from consideration.
- Claims 24-30, 32-33, and 45 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's

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supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (703) 746-5078. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman
Patent Examiner
Art Unit 1652

DS 10/08/03

**DAVID STEADMAN
PATENT EXAMINER**